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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,852	12/06/2001	Nicholas J. Papadopoulos	REG 710-A-US	1613

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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,852	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-100, 104-108, and 132-137* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *137* is/are allowed.

6)☒ Claim(s) *92-100,104-108 and 132-135* is/are rejected.

7)☒ Claim(s) *136* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Jon Lockard.

2. The Amendment filed 18 May 2005 has been received and entered in full. Claims 92 and 105 have been amended, and claims 132-137 have been added. Therefore, claims 92-100, 104-108, and 132-137 are pending and the subject of this Office Action.

3. The terminal disclaimer filed on 18 May 2005 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on Application Number 10/009,852 has been reviewed and is accepted. The terminal disclaimer has been recorded.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

5. The Information Disclosure Statement (IDS) submitted on 18 May 2005 has been considered by the Examiner.

Withdrawn Objections and/or Rejections

6. The objections to the Specification as set forth at page 2 in the previous Office Action (mailed 25 March 2005) are withdrawn in view of Applicant's amendments (filed 18 May 2005).

7. The rejection of claim 92-94, 96-98, 100, and 104-108 under 35 U.S.C. §112, 1st Paragraph (Scope of Enablement), as set forth at pages 2-3 in the previous Office Action (mailed 25 March 2005) is withdrawn in view of Applicants arguments set forth at pages9-10 of the response and in view of the Declaration filed under 37 C.F.R. § 1.132 (filed 18 May 2005). However, new rejections are being applied below.

8. The rejection of claims 92-95, 97-100, 104, 105, and 108 under the judicially created doctrine of obvousness-type double patenting as being unpatentable over claims 1, 4, 7, and 8 of copending Application No. 10/609,775 is withdrawn in view of Applicants submission of a Terminal Disclaimer (filed 18 May 2005).

Maintained and/or New Rejections

Claim Rejections - 35 USC § 112, 1st Paragraph (Scope of Enablement)

9. Claims 92-98, 100, 104-108, and 132-135 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding a fusion protein consisting of an Ig domain 2 of Flt1 and Ig domain 3 of Flk1 and a multimerizing component, wherein the Ig domain 2 of Flt 1 and Ig domain 3 of Flk1 are from human and wherein the fusion protein encoded thereby binds VEGF, does not reasonably provide enablement for nucleic acid molecules encoding a fusion protein comprising an Ig domain 2 of Flt1 and Ig domain 3 of Flk1 and a multimerizing component, wherein the Ig domain 2 of Flt1 an Ig domain 3 of Flk1 are from different species or species other than human, or nucleic acids encoding a fusion protein consisting of an Ig domain 2 of Flt1 and Ig domain 3

of Flk1 and a multimerizing component, wherein the fusion protein encoded thereby does not bind VEGF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

10. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

11. The claims are drawn very broadly to nucleic acid molecules encoding a fusion protein comprising a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor and Ig domain 3 of a second receptor, and a multimerizing component. The claims do not require that (1) the first and second receptors are actually different receptors; (2) the first and second receptors are from the same species, i.e, Ig domain 2 of human Flt1 and Ig domain 3 of zebrafish Flk1; or (3) the encoded fusion protein bind VEGF.

12. While the Specification discloses fusion proteins consisting of an Ig domain 2 of human Flt1 and Ig domain3 of human Flk1 and a multimerizing agent that bind human VEGF, as well as

constructs having the aforementioned domains and multimerizing components in different arrangements, it does not teach a commensurate number of the claimed nucleic acids encoding fusion proteins that bind VEGF that are encompassed by the claims. Based upon the limited number of disclosed nucleic acids and fusion proteins encoded thereby, it is not at all predictable that the claimed nucleic acids would encode fusion proteins that bind VEGF. Furthermore, the Specification does not provide any direction or guidance on how to use the extremely large number of claimed nucleic acids encoding fusion proteins that do not bind VEGF. Undue experimentation would be required of the skilled artisan to use the invention commensurate with the scope of the claims from the written disclosure alone because of the lack of disclosure of the Ig domains from species other than human that would still bind VEGF. Clearly, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st Paragraph (Written Description)

13. Claims 92-98, 100, 104-108, and 132-135 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

14. The claims are drawn very broadly to nucleic acid molecules encoding a fusion protein comprising a vascular endothelial growth factor (VEGF) receptor component having

immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor and Ig domain 3 of a second receptor, and a multimerizing component. The claims do not require that (1) the first and second receptors are actually different receptors; (2) the first and second receptors are from the same species, e.g., an Ig domain 2 of human Flt1 and Ig domain 3 of zebrafish Flk1; or (3) the encoded fusion protein bind VEGF.

15. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a recitation of "Ig domain 2 of a first VEGF receptor" and "Ig domain 3 of a second VEGF receptor". However, there does not appear to be an adequate written description in the specification as filed of any essential structural feature common to molecules that comprise an Ig domain 2 of a first VEGF receptor and an Ig domain 3 of a second VEGF receptor and bind VEGF. The specification discloses three nucleic acids (e.g., SEQ ID NO:11, SEQ ID NO:13, and SEQ ID NO:15) encoding fusion proteins that comprise an Ig domain 2 of a first VEGF receptor and an Ig domain 3 of a second VEGF receptor and bind VEGF. Thus, the disclosure of three species of nucleic acids (all from human) encoding fusion proteins does not appear to provide an adequate written description of the extensive genus of molecules which comprise an Ig domain 2 of a first VEGF receptor and Ig domain 3 of a second receptor, and a multimerizing component and bind VEGF. The

distinguishing characteristics of the claimed genus are not described. The only adequately described species are the nucleic acids set forth in the specification as SEQ ID NO:11, SEQ ID NO:13, and SEQ ID NO:15. Accordingly, the specification does not provide adequate written description of the claimed genus.

16. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

17. With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

18. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

19. Therefore, only an isolated nucleic acid consisting of the sequence of SEQ ID NO: 15, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd Paragraph

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 92-100 and 104-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

22. Claim 92 is rejected as being indefinite because it is unclear if the language of the claim is open or closed. Applicants argue at page 10 of the response (filed 18 May 2005) that the language of the claim limits the claimed fusion protein to those consisting of an Ig domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a mulimerizing component. However, as the claim recites "a fusion protein comprising a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like domains..." the Examiner has interpreted the claim as having open language. Claims 93-100 and 104-108 are rejected for depending from an indefinite claim.

23. Claim 133 is rejected as being indefinite for reciting the phrase "chosen from Flt-1". Since only one receptor is disclosed in the claim, it is unclear what is meant by "chosen from" and thus the metes and bound of the claim cannot be determined. Suggested amendment of the

claim to recite "The isolated nucleic acid molecule of claim 132, wherein the first VEGF receptor is Flt-1", or the like, would be remedial.

Claim Rejections - 35 USC § 102

24. Claims 92-95, 97-98, 100, and 104-108 remain rejected under 35 U.S.C. 102(e) as being anticipated by Davis-Smyth et al. (U.S. Pat. No. 6,100,071) for reasons of record set forth at page 4 of the previous Office Action (mailed 25 March 2005).

25. Claims 92-95, 97-98, and 100 encompass nucleic acid molecules encoding fusion proteins, wherein the fusion protein *comprises* an Ig domain 2 of a first VEGF receptor (including but not limited to Flt1), an Ig domain 3 of a second VEGF receptor (including but not limited to Flk1 and Flt4), and a multimerizing component. The multimerizing component may be an immunoglobulin domain such as the Fc domain of IgG or the heavy chain of IgG. Claims 104-108 are drawn to expression vectors and host-vector systems for producing said fusion proteins.

26. Davis-Smyth et al. teach fusion proteins comprising an immunoglobulin constant region, the Ig domain 2 of Flt1, and the Ig domain 3 of Flt4 (See columns 17, 18, and 27). Davis-Smyth et al. also teach expression vectors and host cells (including E. coli), and methods of producing said fusion proteins (See columns 13 and 14). Thus, in view of the Examiners interpretation of the language of independent claim 92 as being open language i.e., comprising (See 112(2) rejection supra, claims 92-95, 97-98, 100, and 104-108 are anticipated by the reference of Davis-Smyth et al.

27. Applicants argue at page 10 of the response (filed 18 May 2005) that because Davis-Smyth et al. (the '071 patent) does not teach a chimeric receptor with less than all seven Ig-like domains, the '071 patent does not anticipate the invention because the current claims do not encompass sequences which encode receptor molecules comprised of all seven Ig-like domains.

28. Applicants' arguments have been considered but are not found persuasive for the following reasons. As stated in the art rejection made in the previous Office Action (mailed 25 March 2005) and reiterated in the 102(e) rejection above, the Examiner has interpreted the language of independent claim 92 as being open, i.e., "An isolated nucleic acid molecule encoding a fusion protein, *comprising*...". Therefore, claims 92-95, 97-98, 100, and 104-108 are anticipated by the '071 patent.

29. The Examiner has considered Applicants' arguments regarding unexpected results as it relates to a rejection under 35 U.S.C. § 103. However, since no rejection under 35 U.S.C. § 103 is being made at this time, these arguments will not be addressed.

Allowable Subject Matter

30. Claim 136 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

31. Claim 137 is allowable as the prior art does not teach or suggest the particular species of fusion protein-encoding nucleic acid.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
August 31, 2005

ROBERT S. LANDSMAN, PH.D.
PRIMARY EXAMINER